

IN THE CLAIMS

Please amend the claims as follows:

Claim 1 (Previously Presented): A variant of a wild-type mammalian prolactin wherein the variant is an antagonist of a mammalian prolactin receptor, said variant having

a) a mutation or set of mutations within its 14 N-terminal amino acids, wherein said mutation or set of mutations prevents the formation of the disulfide bridge between the cysteine residue at position 4 and the cysteine residue at position 11, and

b) a sterically hindering mutation or set of mutations within binding site 2 of prolactin, wherein said sterically hindering mutation or set of mutations consist in the substitution of at least one residue among Ala₂₂ or Gly₁₂₉, by a residue selected among Tyr, Phe, Asp, Glu, Arg, Lys and Trp;

wherein said wild-type mammalian prolactin has cysteine residues at position 4 and position 11 of the mature prolactin, an alanine residue at position 22 of the mature prolactin, and a glycine residue at position 129 of the mature prolactin;

wherein the above positions and numbered residues correspond to the amino acid sequence of human prolactin.

Claim 2 (Previously Presented): The variant of prolactin according to claim 1, wherein mutation(s) a) comprise the deletion of at least the 4 N-terminal residues of prolactin.

Claim 3 (Previously Presented): The variant of prolactin according to claim 2, wherein mutation(s) a) comprise the deletion of the 9 N-terminal residues of prolactin.

Claim 4 (Previously Presented): The variant of prolactin according to claim 3, having the following mutations:

a deletion of at least the 9 N-terminal residues and up to the 14 N-terminal residues;
and
a G129R substitution.

Claim 5 (Previously Presented): The variant of claim 1, which is a variant of human prolactin that has a human prolactin amino acid sequence except for said mutations.

Claim 6 (Previously Presented): A polynucleotide encoding the prolactin variant of claim 1.

Claim 7 (Previously Presented): An expression cassette comprising the polynucleotide of claim 6.

Claim 8 (Previously Presented): A recombinant vector comprising the polynucleotide of claim 6.

Claim 9 (Previously Presented): A host cell transformed by the polynucleotide of claim 6.

Claim 10 (Withdrawn): A cell, organ, tissue, or transgenic non-human mammal produced by gene transfer of, or transformation with, the polynucleotide of claim 6.

Claim 11 (Withdrawn): A therapeutic composition comprising the polynucleotide of claim 6.

Claim 12 (Withdrawn): A method for treating a disease or disorder involving PRL-mediated effects comprising administering the prolactin variant of claim 1 to a subject in need thereof in an amount sufficient to antagonize the activity of prolactin.

Claim 13 (Previously Presented): A variant of a mammalian prolactin which has the following mutations compared to the corresponding wild-type mammalian prolactin:

a) one or more mutations within the 14 N-terminal amino acids of the corresponding mature wild-type prolactin which prevent the formation of a disulfide bridge between the cysteine residues corresponding to positions 4 and 11 of the mature wild-type prolactin, and

b) at least one sterically hindering substitutional mutation at Ala₂₂ or Gly₁₂₉, or both, of the sequence of binding site 2 of the corresponding wild-type mammalian prolactin;

wherein the mature wild-type mammalian prolactin has cysteine residues at positions 4 and 11, an alanine residue at position 22, and a glycine residue at position 129;

wherein the above positions and numbered residues correspond to the amino acid sequence of human prolactin.

Claim 14 (Previously Presented): The variant of claim 13, which contains a deletion of at least one of the cysteine residues at positions 4 or 11 of the corresponding mature wild-type prolactin.

Claim 15 (Previously Presented): The variant of claim 13, which contains a substitution of a non-cysteine amino acid residue for at least one of the cysteine residues at positions 4 or 11 of the corresponding mature wild-type prolactin.

Claim 16 (Previously Presented): The variant of claim 13, which contains a deletion of 9 to 14 N-terminal amino acid residues of the mature wild-type prolactin.

Claim 17 (Previously Presented): The variant of claim 13, which contains a deletion of 9 to 14 N-terminal amino acid residues of the mature wild-type prolactin and a substitution with arginine of the glycine residue corresponding to position 129 of the mature wild-type prolactin.

Claim 18 (Currently Amended): The variant of claim 13, in which the agonist activity of the prolactin variant on the prolactin receptor is abolished ~~or reduced~~ compared to the corresponding mature wild-type prolactin molecule.

Claim 19 (Previously Presented): The variant of claim 13, which is a variant of human prolactin that has a human prolactin amino acid sequence except for said mutations.

Claim 20 (Withdrawn): A method for treating a disease or disorder involving a prolactin receptor (PRLR)-mediated effect comprising administering the prolactin variant of claim 13 to a subject in need thereof in an amount sufficient to antagonize the activity of prolactin for said receptor.

Claim 21 (New): A polypeptide antagonist of a mammalian prolactin receptor

(a) that does not contain a disulfide bridge between the amino acid residues corresponding to Cys₄ and Cys₁₁ in wild-type prolactin, and

(b) that contains at least one substitution within the amino acid residues of binding site 2 of wild-type prolactin with an amino acid that is larger or charged compared to the corresponding wild-type amino acid residue;

wherein said wild-type mammalian prolactin has cysteine residues at position 4 and position 11 of the mature prolactin, an alanine residue at position 22 of the mature prolactin, and a glycine residue at position 129 of the mature prolactin;

wherein the above positions and numbered residues correspond to the amino acid sequence of human prolactin.

Claim 22 (New): The polypeptide antagonist of claim 21, wherein (a) is a deletion of nine to fourteen N-terminal amino acid residues of wild-type prolactin and (b) consists of the substitution of at least one of Ala₂₂ or Gly₁₂₉ by an amino acid residue selected from the group consisting of Tyr, Phe, Asp, Glu, Arg, Lys and Trp.